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Gastrointestinal Cancer

The Critical Role of Tumor Size in Predicting Prognosis for T1 Colon Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. T1 stage • Colon cancer • Tumor size • Cancer-specific survival • Disease-free survival

Abstract

Background. The role of horizontal growth index of tumor size in survival prediction is still underappreciated in colon cancer because of the identification of vertical infiltration index reflected by T stage. We sought to reveal the impact of T stage on the prognostic and predictive value of tumor size in colon cancer.

Materials and Methods. Data of patients with stage I–III colon cancer were extracted from Surveillance, Epidemiology, and End Results Program (SEER) and Fudan University Shanghai Cancer Center (FUSCC) databases. Harrell's concordance index (c-index) and time-dependent receiver operating characteristic curve (ROC) were used to analyze the discriminative ability of prognostic factors.

Results. Stratified analyses based on T stage found that the increase of T stage significantly and negatively repressed the effect of tumor size on death and recurrence risk. In addition, tumor size showed the greatest hazard ratio of cancer-specific death and relapse in T1 colon cancer. Even more importantly, the discriminatory ability of tumor size outperformed any other widely accepted prognostic clinical features in predicting cancer-specific survival (SEER: c-index 0.637, area under the ROC [AUC] 0.649; FUSCC: c-index 0.673, AUC 0.686) and disease-free survival (FUSCC: c-index 0.645, AUC 0.656) in T1 stage colon cancer.

Conclusion. Tumor size is a critical clinical factor with considerable prognostic and predictive value for T1 colon cancer, and it should be selectively incorporated into the current staging system to facilitate prediction of death and recurrence risk. ***The Oncologist*** 2020;25:244–251

Implications for Practice: To date, no consensus has been reached about the prognostic and predictive value of tumor size in colon cancer. Although tumor size is an independent prognostic factor for patients with colon cancer, the impact of tumor size on death or recurrence risk decreased notably with the increase of T stage. More importantly, the discriminative ability of tumor size outperformed any other clinical factors including N stage in patients with T1 colon cancer. Therefore, tumor size should be recommended to be incorporated into current staging systems to facilitate prognosis prediction for patients with T1 colon cancer.

Introduction

Colon cancer is one of the most common malignant tumors in the world [1]. With the development of therapeutic regimens, the past decades have witnessed a significant improvement in the prognosis of patients with colon cancer. Currently, tumor-node-metastasis (TNM) staging is the most widely accepted system for risk stratification in colon cancer [2]. However, the prognosis of patients within the same TNM stage varies strikingly. Consequently, more prognostic factors easily obtained from daily medical records should be identified to improve prognosis prediction and to individualize treatment strategy for patients with colon cancer.

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Tumor size, defined as the maximal horizontal tumor diameter, has been studied for decades, and large horizontal tumor extent has generally been considered to be negatively associated with prognosis in many solid tumors, including colonic malignancies [3–13]. However, because of the vertical index of infiltration depth reflected by T stage, tumor size has not been recognized as a valuable factor in predicting prognosis in colon cancer. Indeed, T stage is a robust risk factor in colon cancer, but no previous studies have clarified the impact of T stage on the independent prognostic role and predictive ability of tumor size. Moreover, as an important horizontal tumor growth index, tumor size may have a unique role in specific subgroup of colon cancer with certain infiltration depth.

In this study, we analyzed the prognostic value of tumor size and compared its prognostic accuracy with other widely accepted factors in colon cancer with different T stage using data extracted from the Surveillance, Epidemiology, and End Results (SEER)–registered database. Moreover, because SEER data lack information about complete preoperative treatment and quality of operation, we further validated the results from SEER database in Fudan University Shanghai Cancer Center Database (FUSCC).

Subjects, Materials, and Methods

Patient Selection in the SEER Database

Patient data were obtained from the SEER database (http://seer.cancer.gov/seerstat), which is sponsored by the U.S. National Cancer Institute. It currently collects and publishes cancer incidence and survival data covering 18 population-based cancer registries that represent approximately 28% of the population in the U.S. Using the SEER database, we identified a total of 121,926 primary colon cancers diagnosed between 2010 and 2014. Patients who met the following criteria were included: (A) pathologically diagnosed colon cancer; (B) patients received major surgical resection; (C) histological types were limited to adenocarcinoma (8140/3, 8210/3, 8261/3, 8263/3), mucinous adenocarcinoma (8480/3), and signet-ring cell carcinoma (8490/3); (D) American Joint Committee on Cancer (AJCC) stage I–III; and (E) colon cancer was the only primary tumor. Patients with unknown information of detailed AJCC stage, tumor size, and follow-up were excluded. Finally, a total of 52,513 patients were identified from SEER database in this study.

Patient Selection in the FUSCC Database

Patients with colon cancer diagnosed from 2006 to 2015 in FUSCC were identified in the present study. The inclusion criteria were as follows: (A) pathologically diagnosed colon cancer; (B) patients received radical surgical resection; (C) histological types were limited to adenocarcinoma (8140/3, 8210/3, 8261/3, 8263/3), mucinous adenocarcinoma (8480/3), and signet-ring cell carcinoma (8490/3); (D) AJCC stage I–III; (E) colon cancer was the only primary tumor; and (F) patients were not treated with preoperative chemotherapy or endoscopic resection. After exclusion, a total of 4,398 patients with colon cancer were identified. The study was approved by the Ethical Committee and Institutional Review Board of the FUSCC, and written informed consent was signed by all the patients in FUSCC.

Statistical Analysis

Demographic and clinicopathological variables of age, gender, grade, tumor site, tumor size, T and N stage, adjuvant therapy regimens, and regional lymph node harvest (LNH) were retrieved from the SEER database. Furthermore, preoperative carcinoembryonic antigen (CEA) level, peripheral nerve invasion, and lymph-vascular invasion were also extracted from FUSCC database. All included patients were restaged based on the AJCC Cancer Staging Manual (8th edition). Tumor size was analyzed as continuous variable in this study. Cancer-specific survival (CSS) was the primary endpoint for the analysis based on both SEER and FUSCC database. As disease-free survival (DFS) was available in FUSCC, DFS was also set as another primary endpoint. DFS was defined as the time from surgical treatment to first recurrence or end of life, and CSS represented the time period from treatment to death from colon cancer. The survival data of patients from FUSCC cohort were provided by the Clinical Statistics Center of FUSCC, relying on the hospital medical records follow-up platform or contacts with patients by phone or e-mail. Patients whose death or relapse status information during the follow-up period was not available and patients who were still alive or absent any relapse at last follow-up were censored for survival analysis.

Univariate analysis was utilized to examine the parameters that are significantly associated with CSS and DFS. A multivariate Cox proportional hazards model was built to verify the independent role of prognostic factors. The discriminative ability of tumor size and other factors were evaluated by using the Harrell's concordance index (c-index) and time-dependent receiver operating characteristic curve (ROC) [14, 15]. A predictive variable with a higher c statistic and area under the ROC (AUC) indicated a better discrimination ability or prognostic accuracy. AUC at 5 years was analyzed and used in this study. Two-sided $p < .05$ was considered statistically significant. All of the statistical analyses were performed with R (version 3.2.5, www.r-project.org).

Results

Patient Characteristics

Among 52,513 patients identified from the SEER database, 16,598 (31.6%) patients were aged less than 60 years. Of the patients, 27,033 (51.5%) were female, and 25,480 (48.5%) were male. Diagnoses were as follows: 27,286 (52.0%) patients were diagnosed with right-side colon cancer, 5,218 (9.9%) with transverse colon cancer, and 20,009 (38.1%) with left-side colon cancer. Grading was as follows: 4,559 (8.7%) patients had grade I, 37,556(71.5%) were grade II, and 9,390 (17.9%) were grade III or IV colon cancer. Distributions of colon cancer in adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma were 47,529 (90.5%), 4,432 (8.4 %), and 552 (1.1%), respectively. The proportions of N0, N1a, N1b, N1c, N2a, and N2b stage were 61.8%, 11.6%, 11.5%, 2.4%, 7%, and 5.7%, respectively. The median (interquartile range) of tumor size was 4.1 (2.8–6.0) cm. Similar

Table 1. Baseline clinicopathological features of patients with colon cancer stratified by T stage in SEER and FUSCC data sets

	SEER, *n* (%)					FUSCC, *n* (%)				
Features	**All**	**T1**	**T2**	**T3**	**T4**	**All**	**T1**	**T2**	**T3**	**T4**
Age, years										
≤60	16,598 (31.6)	2,404 (34.89)	2,424 (28.38)	9,157 (31.27)	2,613 (33.49)	1,921 (43.68)	109 (49.19)	214 (47.63)	883 (42.33)	715 (43.56)
>60	35,915 (68.4)	4,487 (65.11)	6,116 (71.62)	20,122 (68.73)	5,190 (66.51)	2,477 (56.32)	113 (50.81)	235 (52.37)	1,203 (57.67)	926 (56.44)
Sex										
Female	27,033 (51.5)	3,347 (48.57)	4,495 (52.63)	15,052 (51.41)	4,139 (53.04)	1,736 (39.48)	104 (46.68)	212 (47.13)	810 (38.82)	611 (37.24)
Male	25,480 (48.5)	3,544 (51.43)	4,045 (47.37)	14,227 (48.59)	3,664 (46.96)	2,662 (60.52)	118 (53.32)	237 (52.87)	1,276 (61.18)	1,030 (62.76)
Location										
Right	27,286 (52)	3,062 (44.43)	4,780 (55.97)	15,288 (52.21)	4,156 (53.26)	2,101 (47.8)	88 (39.6)	175 (39)	1,069 (51.2)	769 (46.9)
Transverse	5,218 (9.9)	605 (8.78)	730 (8.55)	3,136 (10.71)	747 (9.57)	213 (4.8)	9 (4.1)	22 (4.9)	97 (4.7)	85 (5.2)
Left	20,009 (38.1)	3,224 (46.79)	3,030 (35.48)	10,855 (37.07)	2,900 (37.17)	2,084 (47.4)	125 (56.3)	252 (56.1)	920 (44.1)	787 (48)
Grade										
I	4,559 (8.7)	1,464 (21.25)	862 (10.09)	1,823 (6.23)	410 (5.25)	338 (7.7)	92 (41.4)	73 (16.3)	110 (5.3)	63 (3.8)
II	37,556 (71.5)	4,600 (66.75)	6,677 (78.19)	21,476 (73.35)	4,803 (61.55)	3,572 (81.2)	114 (51.4)	352 (78.4)	1,759 (84.3)	1,347 (82.1)
III/IV	9,390 (17.9)	451 (6.54)	885 (10.36)	5,608 (19.15)	2,446 (31.35)	357 (8.1)	3 (1.4)	13 (2.9)	167 (8)	174 (10.6)
Unknown	1,008 (1.9)	376 (5.46)	116 (1.36)	372 (1.27)	144 (1.85)	131 (3)	13 (5.9)	11 (2.4)	50 (2.4)	57 (3.5)
Histology										
AC	47,529 (90.5)	6,703 (97.27)	7,958 (93.19)	26,307 (89.85)	6,561 (84.08)	3,636 (82.7)	218 (98.2)	409 (91.1)	1,696 (81.3)	1,313 (80)
MAC	4,432 (8.4)	170 (2.47)	552 (6.46)	2,691 (9.19)	1,019 (13.06)	679 (15.4)	4 (1.8)	39 (8.7)	348 (16.7)	288 (17.6)
SRCC	552 (1.1)	18 (0.26)	30 (0.35)	281 (0.96)	223 (2.86)	83 (1.9)	0 (0)	1 (0.2)	42 (2)	40 (2.4)
LNH										
<12	7,833 (14.9)	2,328 (33.78)	1,336 (15.64)	3,176 (10.85)	993 (12.73)	443 (10.1)	65 (29.3)	68 (15.1)	121 (5.8)	189 (11.5)
≥12	44,680 (85.1)	4,563 (66.22)	7,204 (84.36)	26,103 (89.15)	6,810 (87.27)	3,955 (89.9)	157 (70.7)	381 (84.9)	1,965 (94.2)	1,452 (88.5)
N stage										
N0	32,431 (61.8)	6,196 (89.91)	6,876 (80.52)	16,297 (55.66)	3,062 (39.24)	2,462 (56)	200 (90.1)	350 (78)	1,180 (56.6)	732 (44.6)
N1a	6,079 (11.6)	385 (5.59)	768 (8.99)	3,814 (13.03)	1,112 (14.25)	531 (12.1)	14 (6.3)	51 (11.4)	258 (12.4)	208 (12.7)
N1b	6,062 (11.5)	217 (3.15)	528 (6.18)	4,086 (13.96)	1,231 (15.78)	620 (14.1)	5 (2.3)	26 (5.8)	300 (14.4)	289 (17.6)
N1c	1,282 (2.4)	28 (0.41)	84 (0.98)	837 (2.86)	333 (4.27)	355 (8.1)	2 (0.9)	8 (1.8)	157 (7.5)	188 (11.5)
N2a	3,680 (7)	54 (0.78)	209 (2.45)	2,439 (8.33)	978 (12.53)	293 (6.7)	1 (0.5)	8 (1.8)	127 (6.1)	157 (9.6)
2b	2,979 (5.7)	11 (0.16)	75 (0.88)	1,806 (6.17)	1,087 (13.93)	137 (3.1)	0 (0)	6 (1.3)	64 (3.1)	67 (4.1)
CEA level										
Low	NA	NA	NA	NA	NA	2,799 (63.6)	196 (88.7)	368 (82)	1,282 (61.5)	953 (58.1)
High	NA	NA	NA	NA	NA	1,599 (36.4)	25 (11.3)	81 (18)	804 (38.5)	688 (41.9)

(continued)

Table 1. (continued)

Features	SEER, *n* (%)					FUSCC, *n* (%)				
	All	T1	T2	T3	T4	All	T1	T2	T3	T4
LVI										
No	NA	NA	NA	NA	NA	3,300 (75)	204 (92.3)	389 (86.6)	1,556 (74.6)	1,151 (70.1)
Yes	NA	NA	NA	NA	NA	1,098 (25)	17 (7.7)	60 (13.4)	530 (25.4)	490 (29.9)
PNI										
No	NA	NA	NA	NA	NA	3,455 (78.6)	215 (97.3)	431 (96)	1,582 (75.8)	1,227 (74.8)
Yes	NA	NA	NA	NA	NA	943 (21.4)	6 (2.7)	18 (4)	504 (24.2)	414 (25.2)
Tumor size, median (IQR)	4.1 (2.8–6.0)	1.4 (0.7–2.4)	3.3 (2.4–4.5)	4.6 (3.5–6.1)	5.5 (4.0–7.5)	4.0 (3.0–6.0)	2.0 (1.5–3.0)	3.5 (2.5–4.5)	4.5 (3.5–6.0)	5.0 (3.5–6.5)

Abbreviations: AC, adenocarcinoma; CEA, carcinoembryonic antigen; FUSCC, Fudan University Shanghai Cancer Center; IQR, interquartile range; LNH, lymph node harvest; LVI, lymph-vascular invasion; MAC, mucinous adenocarcinoma; NA, not available; PNI, peripheral nerve invasion; SEER, Surveillance, Epidemiology, and End Results; SRCC, signet-ring cell carcinoma.

distribution of features was observed in patients from the FUSCC database. However, the incidence of male patients was notably higher in the FUSCC database. Detailed information about clinical pathological features is shown in Table 1.

Impact of T Stage on the Prognostic Value of Tumor Size

Univariate and multivariate Cox regression models were used to evaluate the prognostic value of the tumor size. The results of the Cox regression analysis conducted in all the patients and stratified by T stage are illustrated in Figure 1. In all the patients, tumor size was an independent prognostic factor both in the SEER and FUSCC data sets. Large tumor size was negatively associated with death and recurrence risk (Fig. 1).

In the SEER data set, subgroup analysis based on T stage found that the independent prognostic role of tumor size was not influenced by T stage, but its impact on death risk reflected by hazard ratio (HR) decreased strikingly with the increment of T stage (Fig. 1A). In the FUSCC cohort, T stage did not influence the independent value of tumor size in predicting CSS either (Fig. 1B). However, tumor size was no longer a prognosis predictor in T4 colon cancer (Fig. 1C). Similar to the results from the SEER data set, the impact of tumor size on both death and relapse risk declined dramatically with increase of infiltration depth (Fig. 1B, C). In summary, tumor size was associated with the greatest impact on death and relapse risk in T1 colon cancer, whereas the impact of tumor size on death or relapse risk decreased aberrantly in T4 colon cancer.

Discriminatory Ability of Tumor Size Outperformed Any Other Clinical Factors in T1 Stage

C-index and time-dependent ROC were used to evaluate the predictive ability of clinical factors in the SEER and FUSCC data sets. Overall, among all the patients with stage I–III colon cancer, N stage is expectedly the best predictor for CSS (SEER: c-index 0.667, AUC 0.689; FUSCC: c-index 0.686, AUC 0.637) and DFS (c-index 0.677, AUC 0.642) with the highest c-index and AUC (Table 2). Compared with N stage, tumor size did perform more poorly in predicting CSS (SEER: c-index 0.618, AUC 0.608; FUSCC: c-index 0.563, AUC 0.527) and DFS (c-index 0.548, AUC 0.511; Table 2). Further subgroup analyses based on T stage were conducted, and we found that in patients with stage T1 colon cancer, tumor size outperformed any other factors in predicting CSS (SEER: c-index 0.637, AUC 0.649; FUSCC: c-index 0.673, AUC 0.686) and DFS (c-index 0.645, AUC 0.656) with a considerable predictive ability, whereas N stage failed to be a good predictor for CSS (SEER: c-index 0.525, AUC 0.563; FUSCC: c-index 0.599, AUC 0.618) and DFS (c-index 0.531, AUC 0.601). However, once T stage increased over T1 stage, the predictive ability of tumor size reduced dramatically and even became negligible (Table 2). In contrast, the predictive ability of N stage increased significantly after T stage became more advanced than T1 (Table 2).

To further clarify the predictive value of tumor size in T1 colon cancer, we stratified patients with stage T1 colon cancer into two groups based on lymph node status in SEER database. It is suggested that tumor size performed best

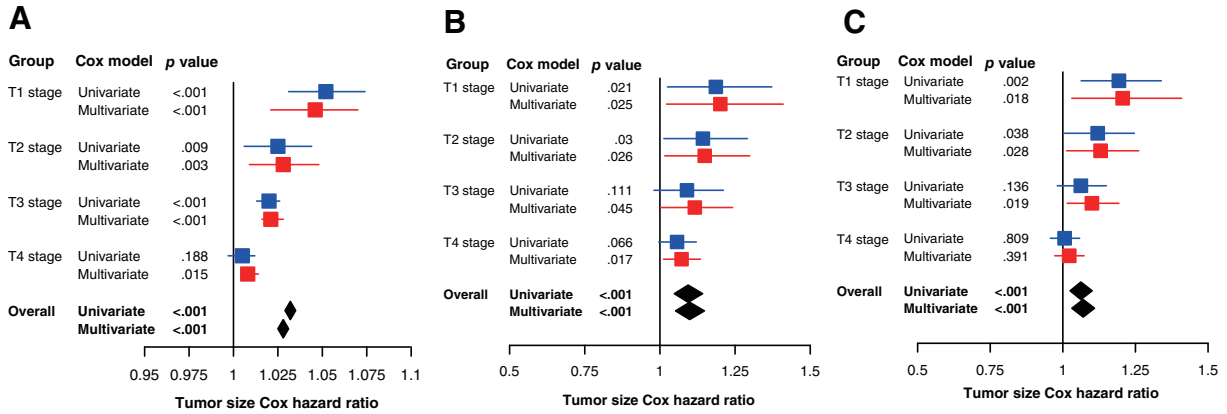

Figure 1. Impact of T stage on the hazard ratio of tumor size in predicting CSS and DFS of colon cancer. **(A):** CSS in SEER database. **(B):** CSS in FUSCC database. **(C):** DFS in FUSCC database.
Abbreviations: CSS, cancer-specific survival; DFS, disease-free survival; FUSCC, Fudan University Shanghai Cancer Center; SEER, Surveillance, Epidemiology, and End Results.

Table 2. Discriminatory ability of clinicopathological factors in predicting survival in colon cancer

	All		T1		T2		T3		T4	
Variables	**C-index**	**AUC**	**C-index**	**AUC**	**C-index**	**AUC**	**C-index**	**AUC**	**C-index**	**AUC**
SEER-CSS										
Tumor size	0.618	0.608	0.637	0.649	0.535	0.534	0.535	0.509	0.532	0.489
N stage	0.667	0.689	0.525	0.563	0.584	0.605	0.63	0.651	0.615	0.649
Grade	0.588	0.574	0.551	0.542	0.538	0.534	0.549	0.536	0.583	0.569
Histology	0.523	0.521	0.51	0.506	0.503	0.493	0.511	0.508	0.512	0.508
Location	0.533	0.513	0.529	0.534	0.542	0.52	0.524	0.502	0.539	0.513
LNH	0.52	0.512	0.549	0.51	0.547	0.544	0.534	0.53	0.536	0.528
FUSCC-CSS										
Tumor size	0.563	0.527	0.673	0.686	0.521	0.569	0.548	0.509	0.533	0.487
N stage	0.686	0.637	0.599	0.618	0.578	0.581	0.666	0.645	0.678	0.635
Grade	0.581	0.556	0.623	0.466	0.628	0.59	0.55	0.556	0.572	0.553
Histology	0.543	0.529	0.508	0.489	0.54	0.531	0.515	0.506	0.544	0.53
Location	0.549	0.533	0.546	0.488	0.694	0.515	0.571	0.505	0.549	0.538
LNH	0.537	0.523	0.492	0.455	0.574	0.542	0.516	0.514	0.549	0.539
CEA	0.593	0.589	0.633	0.493	0.623	0.627	0.608	0.589	0.562	0.563
LVI	0.611	0.593	0.622	0.548	0.562	0.426	0.574	0.539	0.619	0.609
PNI	0.569	0.576	0.579	0.51	0.504	0.502	0.585	0.599	0.548	0.554
FUSCC-DFS										
Tumor size	0.548	0.511	0.645	0.656	0.539	0.533	0.551	0.544	0.507	0.463
N stage	0.677	0.642	0.531	0.601	0.576	0.527	0.699	0.639	0.645	0.628
Grade	0.567	0.548	0.59	0.333	0.594	0.607	0.569	0.552	0.549	0.539
Histology	0.53	0.518	0.508	0.489	0.561	0.545	0.527	0.506	0.52	0.512
Location	0.521	0.521	0.53	0.51	0.534	0.478	0.533	0.523	0.516	0.519
LNH	0.529	0.523	0.613	0.506	0.555	0.551	0.504	0.512	0.539	0.537
CEA	0.604	0.589	0.58	0.518	0.634	0.637	0.645	0.626	0.564	0.555
LVI	0.595	0.595	0.525	0.539	0.543	0.451	0.565	0.539	0.604	0.611
PNI	0.579	0.591	0.528	0.502	0.519	0.477	0.59	0.578	0.562	0.581

Abbreviations: AUC, area under the receiver operating characteristic curve; CEA, carcinoembryonic antigen; CSS, cancer-specific survival; DFS, disease-free survival; FUSCC, Fudan University Shanghai Cancer Center; LNH, lymph node harvest; LVI, lymph-vascular invasion; PNI, peripheral nerve invasion; SEER, Surveillance, Epidemiology, and End Results.

Table 3. Discriminative power of prognostic factors in T1 colon cancer from the Surveillance, Epidemiology, and End Results database

	T1N0 stage		T1N+ stage	
Variables	**C-index**	**AUC**	**C-index**	**AUC**
Tumor size	0.626	0.648	0.682	0.625
N stage	0.5	0.5	0.541	0.571
Grade	0.532	0.531	0.634	0.56
Histology	0.507	0.497	0.522	0.527
Location	0.531	0.532	0.599	0.577
LNH	0.545	0.511	0.603	0.558

Abbreviations: AUC, area under the receiver operating characteristic curve; LNH, lymph node harvest.

among all the factors regardless of lymph node status and maintained its good discriminative ability in both groups (Table 3). This further stratified analysis was not conducted in the FUSCC cohort because of sample size limitation.

In summary, tumor size, in T1 colon cancer, showed a considerable predictive ability and outperformed any other widely used clinical factors, as compared with colon cancers of higher T stage.

Construction and Validation of Tumor Size–Based Nomogram in T1 Colon Cancer

To facilitate the clinical application of tumor size in survival prediction for patients with stage T1 colon cancer, we categorized tumor size according to its quartile and developed a nomogram in SEER data set based on multivariate Cox analysis. Tumor size (categorical), age, N stage, grade, and LNH were incorporated into this nomogram (Fig. 2A). Harrell's c-index of this nomogram for CSS prediction in SEER was 0.710 (95% confidence interval, 0.628–0.791). Time-dependent ROC suggested that the nomogram incorporating tumor size was significantly more accurate in predicting CSS than the model without tumor size (AUC at 5 years: 0.701 vs. 0.643; Fig. 2C).

FUSCC cohort was further used to validate the predictive efficiency of the nomogram developed in the SEER database. These data suggested that a tumor size–based nomogram can predict CSS in FUSCC with a good discriminative ability, but absence of tumor size will notably decrease the prognostic accuracy (Fig. 2D).

Discussion

In this present study, the large population-based SEER database and FUSCC database were used to analyze the impact of T stage on the prognostic and predictive value of tumor size in colon cancer. We demonstrated here that increase of T stage will significantly reduce the impact of tumor size on death and recurrence risk of colon cancer. In addition, tumor size outperformed any other clinical factors and showed the best discriminative ability in patients with stage T1 colon cancer but showed dramatically weakened discriminatory power in predicting CSS and DFS in patients with more advanced T stage.

Previous studies suggested that solid tumors including gastrointestinal tumors can obtain the potential of dissemination during the process of growing both horizontally and vertically [16]. Currently, although many investigators have confirmed the negative prognostic role of tumor size, the value of tumor size in survival prediction is still underappreciated [3–13]. However, the vertical growth index reflected by T stage has been established as one of the dominating prognostic factors and has been incorporated into the widely accepted TNM staging system in colon cancer. Therefore, although both are a growth index, vertical infiltration seems to be much more important than horizontal proliferation, which might explain why the prognostic prediction value of tumor size dwindled as the T stage became more advanced. Like many previous studies [6, 8, 10, 17], we confirmed the independent predictive effect of tumor size in prognosis among all patients with stage I–III colon cancer. However, the HR of tumor size decreased gradually with the increase of T stage. In other words, more advanced tumor infiltration will weaken the risk impact on prognosis of larger tumor size. Similar results were found in the predictive power analysis. More advanced T stage is also able to negatively influence the survival predictive ability of tumor size. Once the tumor infiltrates into the muscular layer, the discriminative ability decreases dramatically.

One of the most important reasons for the negative impact of T stage on tumor size could be the inaccurate calculation of tumor size. It is imaginable that for the tumors with advanced stage, accurate measurement of tumor size is difficult because the invasion extent of the bowel wall might be larger than the maximal diameter of the cancerous extent on the mucosa. Therefore, merely the maximal horizontal diameter cannot exactly characterize the tumor growth extent with advanced infiltration. On the other hand, for the tumors restricted to the submucosa, growing into the lumen may be the main growth pattern, and the tumor size measured at this stage will be the dominant index that depicts the growth of tumor. Even so, we believe there are many other underlying causes for the impact on tumor size necessitating clarification.

An exciting result revealed in this study is that tumor size performed the best in survival prediction among many widely accepted clinical features in T1 stage colon cancer. T1 colon cancer is always characterized as an early stage tumor with favorable prognosis. Its long-term survival depends mainly upon the lymph node status, with a colorectal cancer–specific 5-year survival of ≥95% in the absence of metastatic lymph node and 68%–90% in the presence of positive lymph node [18, 19]. However, the positive rate of lymph node was reported only in 8%–12% of patients [20, 21]. In this present study, the lymph node metastatic rate was only 10.1% and 9.9% in patients with stage T1 colon cancer from SEER and FUSCC data sets, and less than 1% of patients were categorized as N2 stage. Consequently, it is reasonable to find that the discriminatory ability of N stage was weak in T1 colon cancer. Therefore, the predictive value of N stage should be reappraised according to T stage. Actually, in addition to N stage, many other predefined high-risk clinical features, including poor differentiation, mucinous histology, and high CEA level, were infrequently found in T1 stage colon cancer [22–25]. Hence, using these factors alone to predict survival of T1 stage colon cancer may not be reliable.

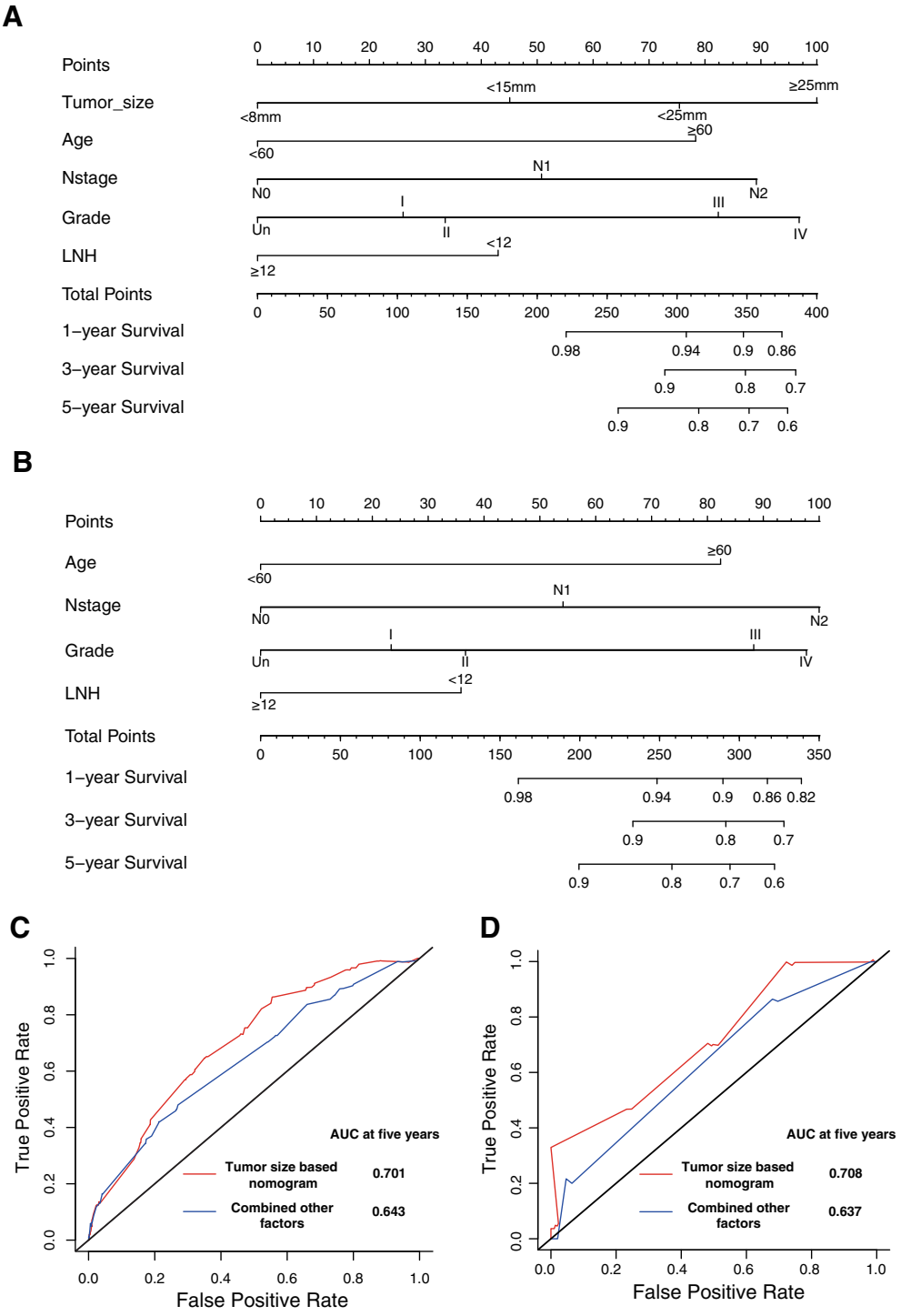

Figure 2. Construction and validation of tumor size–based nomogram in T1 colon cancer. **(A):** Tumor size–based nomogram in Surveillance, Epidemiology, and End Results (SEER) data set. **(B):** Nomogram without tumor size in SEER. **(C):** Time-dependent ROC of the nomogram with or without tumor size. **(D):** Validation and prediction performance of the nomogram with or without tumor size in Fudan University Shanghai Cancer Center cohort.
Abbreviations: AUC, area under the ROC; LNH, lymph node harvest; ROC, receiver operating characteristic curve.

To the best of our knowledge, the present study is one of the first study evaluating the impact of T stage on the prognostic and predictive value of tumor size in colon cancer. In addition, we revealed the critical role of tumor in predicting survival in T1 colon cancer. However, several limitations cannot be avoided completely in our study. To begin with, this study is a retrospective analysis, and selection bias could not be completely avoided. Furthermore, although this study was conducted in two large population databases, the proportion of T1 stage colon cancer is still

too small in Chinese patients from the FUSCC database; thus, future multicenter studies are warranted to validate the results presented in this study.

Conclusion

The prognostic and predictive value of tumor size varied in patients with different T stages. The impact of tumor size on death and recurrence risk decreases gradually with the increment of T stage. More intriguingly, in patients with stage T1 colon cancer, tumor size possesses a better discriminative ability than any other established prognostic factors.

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Disclosures

The authors indicated no financial relationships.

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